09/9118,146

Paul Epstein

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L2

(FILE 'HOME' ENTERED AT 16:54:54 ON 23 NOV 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 16:55:09 ON 23 NOV 2004

L1 2631 S C57BL6

774605 S DIABETES OR DIABETIC OR HYPERGLYCEMIA OR HYPOINSULIN?

L3 110 S L1 AND L2

L4 2 S REVIEW AND L3

L5 50 DUP REM L3 (60 DUPLICATES REMOVED)

L6 2 DUP REM L4 (0 DUPLICATES REMOVED)

=> d au ti so pi ab 1-2 16

L6 ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

AU Fukai, Tohru [Reprint author]; Folz, Rodney J.; Landmesser, Ulf; Harrison, David G.

TI Extracellular superoxide dismutase and cardiovascular disease.

SO Cardiovascular Research, (1 August, 2002) Vol. 55, No. 2, pp. 239-249. print.

CODEN: CVREAU. ISSN: 0008-6363.

- AB Excessive production and/or inadequate removal of reactive oxygen species, especially superoxide anion (O2.-), have been implicated in the pathogenesis of many cardiovascular diseases, including atherosclerosis, hypertension, diabetes, and in endothelial dysfunction by decreasing nitric oxide (NO) bioactivity. Since the vascular levels of O2.- are regulated by the superoxide dismutase (SOD) enzymes, a role of SOD in the cardiovascular disease is of substantial interest. Particularly, a major form of SOD in the vessel wall is the extracellular SOD (ecSOD). This review will discuss the characteristics of ecSOD and the role of ecSOD in cardiovascular diseases.
- L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

AU Van Tol, Arie

- TI Phospholipid transfer protein
- SO Current Opinion in Lipidology (2002), 13(2), 135-139 CODEN: COPLEU; ISSN: 0957-9672
- A review. A role for phospholipid transfer protein (PLTP) in HDL remodelling and in the formation of pre- $\beta$ -HDL is now well established, both in vivo and in vitro. Over-expression of human PLTP in C57BL6 mice lowers plasma HDL levels, probably because of increased HDL catabolism. Despite these low HDL levels, plasma from these mice mitigates cholesterol accumulation in macrophages and has increased potential for pre- $\beta$ -HDL formation. Plasma HDL concentration is also decreased in PLTP knockout mice. These intriguing observations can be explained by recent studies that indicate that PLTP is not only involved in remodelling of HDL subfractions but also in VLDL turnover. The role of PLTP in atherogenesis and VLDL synthesis was demonstrated in transgenic mouse models with increased susceptibility for the development of atherosclerosis, bred into PLTP knockout mice. The data clearly show that PLTP can be proatherogenic. As mentioned above, however, PLTP may have antiatherogenic potential in wild-type C57BL6 mice. Information regarding the role and regulation of PLTP in human (patho)physiol. is still relatively sparse but accumulating rapidly. PLTP activity is elevated in diabetes mellitus (both type 1 and type 2), obesity and insulin resistance.

<sup>=&</sup>gt; d au ti so 1-50 15

L5 ANSWER 1 OF 50 MEDLINE on STN DUPLICATE 1
AU Zou Ming-Hui; Kirkpatrick Stacy S; Davis Bradley J; Nelson John S; Wiles

- Walter G 4th; Schlattner Uwe; Neumann Dietbert; Brownlee Michael; Freeman Michael B; Goldman Mitch H
- TI Activation of the AMP-activated protein kinase by the antidiabetic drug metformin in vivo. Role of mitochondrial reactive nitrogen species.
- SO Journal of biological chemistry, (2004 Oct 15) 279 (42) 43940-51. Journal code: 2985121R. ISSN: 0021-9258.
- L5 ANSWER 2 OF 50 MEDLINE on STN DUPLICATE 2
- AU Cooksey Robert C; Jouihan Hani A; Ajioka Richard S; Hazel Mark W; Jones Deborah L; Kushner James P; McClain Donald A
- Oxidative stress, beta-cell apoptosis, and decreased insulin secretory capacity in mouse models of hemochromatosis.
- SO Endocrinology, (2004 Nov) 145 (11) 5305-12. Journal code: 0375040. ISSN: 0013-7227.
- L5 ANSWER 3 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Nicol, Christopher J.; Yoon, Michung; Ward, Jerrold M.; Yamashita, Masamichi; Fukamachi, Katsumi; Peters, Jeffrey M.; Gonzalez, Frank J. [Reprint Author]
- TI PPARgamma influences susceptibility to DMBA-induced mammary, ovarian and skin carcinogenesis.
- SO Carcinogenesis (Oxford), (September 2004) Vol. 25, No. 9, pp. 1747-1755. print.

  CODEN: CRNGDP. ISSN: 0143-3334.
- L5 ANSWER 4 OF 50 MEDLINE on STN DUPLICATE 3
- AU Luan Hongmei; Leitges Michael; Gupta Rita R; Pacheco Daniel; Seidner Andres; Liggett Jessica; Ito Yasuki; Kowluru Renu; Berkowitz Bruce A
- TI Effect of PKCbeta on retinal oxygenation response in experimental diabetes.
- SO Investigative ophthalmology & visual science, (2004 Mar) 45 (3) 937-42. Journal code: 7703701. ISSN: 0146-0404.
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- AU Bolduc C; Larose M; Yoshioka M; Ye P; Belleau P; Labrie C; Morissette J; Raymond V; Labrie F; St-Amand J
- TI Effects of dihydrotestosterone on adipose tissue measured by serial analysis of gene expression.
- SO Journal of molecular endocrinology, (2004 Oct) 33 (2) 429-44. Journal code: 8902617. ISSN: 0952-5041.
- L5 ANSWER 6 OF 50 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Matzelle M M; Babensee J E (Reprint)
- Humoral immune responses to model antigen co-delivered with biomaterials used in tissue engineering
- SO BIOMATERIALS, (JAN 2004) Vol. 25, No. 2, pp. 295-304.
  Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON,
  OXFORD OX5 1GB, OXON, ENGLAND.
  ISSN: 0142-9612.
- L5 ANSWER 7 OF 50 MEDLINE on STN DUPLICATE 5
- AU Rooman I; Bouwens L
- TI Combined gastrin and epidermal growth factor treatment induces islet regeneration and restores normoglycaemia in C57B16/J mice treated with alloxan.
- SO Diabetologia, (2004 Feb) 47 (2) 259-65. Journal code: 0006777. ISSN: 0012-186X.
- L5 ANSWER 8 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Rao, Reena [Reprint Author]; Zhang, Mingzhi; Breyer, Matthew D; Hao,

Chuanming

- TI Role of Cyclooxygenase 2 induction in Lithium (Li+) Induced polyuria.
- SO FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 673.28. http://www.fasebj.org/. e-file.
  Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB. ISSN: 0892-6638 (ISSN print).
- L5 ANSWER 9 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Langston, John W [Reprint Author]; Lefer, David J
- TI Acute Metformin Therapy Protects the Liver Against Ischemia-Reperfusion Injury.
- SO FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 441.2. http://www.fasebj.org/. e-file.
  Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB. ISSN: 0892-6638 (ISSN print).
- L5 ANSWER 10 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Cardozo, A. K.; Proost, P.; Gysemans, C.; Chen, M.-C.; Mathieu, C.; Eizirik, D. L. [Reprint Author]
- TI IL-1beta and IFN-gamma induce the expression of diverse chemokines and IL-15 in human and rat pancreatic islet cells, and in islets from pre-diabetic NOD mice.
- SO Diabetologia, (February 2003) Vol. 46, No. 2, pp. 255-266. print. CODEN: DBTGAJ. ISSN: 0012-186X.
- L5 ANSWER 11 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Kang, Elizabeth M. [Reprint Author]; Zickler, Philipp P. [Reprint Author]; Burns, Sean [Reprint Author]; Langemeijer, Saskia [Reprint Author]; Seufert, Caleb [Reprint Author]; Patterson, Noelle; Harlan, David; Tisdale, John F. [Reprint Author]
- TI Hematopoietic stem cell transplantation allows for tolerance of allogeneic islets but does not significantly contribute to organ regeneration.

  SO Blood (November 16 2003) Vol. 100 Windows for tolerance of allogeneic islets but does not significantly contribute to organ regeneration.
- Blood, (November 16 2003) Vol. 102, No. 11, pp. 213a. print.

  Meeting Info.: 45th Annual Meeting of the American Society of Hematology.

  San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.

  CODEN: BLOOAW. ISSN: 0006-4971.
- L5 ANSWER 12 OF 50 MEDLINE on STN DUPLICATE 6
- AU Shankar Kartik; Vaidya Vishal S; Wang Tao; Bucci Thomas J; Mehendale Harihara M
- TI Streptozotocin-induced diabetic mice are resistant to lethal effects of thioacetamide hepatotoxicity.
- Toxicology and applied pharmacology, (2003 Apr 15) 188 (2) 122-34. Journal code: 0416575. ISSN: 0041-008X.
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- TI Enteroinsular axis of db/db mice and efficacy of dipeptidyl peptidase IV inhibition.
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- AU Zhang, Li [Reprint Author]; Renaud, Jean-Marc
- TI KATP channel-deficient mice are streptozotocin resistant.
- SO FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 570.4. http://www.fasebj.org/. e-file.

Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB. ISSN: 0892-6638 (ISSN print).

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- ANSWER 16 OF 50 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation.  $L_5$ on STN
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- Somatostatin analogs inhibit neonatal retinal neovascularization TI
- EXPERIMENTAL EYE RESEARCH, (MAY 2002) Vol. 74, No. 5, pp. 553-559. Publisher: ACADEMIC PRESS LTD ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0014-4835.
- ANSWER 17 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. L5 STN
- Fukai, Tohru [Reprint author]; Folz, Rodney J.; Landmesser, Ulf; Harrison, ΑU David G.
- Extracellular superoxide dismutase and cardiovascular disease. TΙ
- Cardiovascular Research, (1 August, 2002) Vol. 55, No. 2, pp. 239-249. SO print. CODEN: CVREAU. ISSN: 0008-6363.
- L5 ANSWER 18 OF 50 MEDLINE on STN

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- ΑU van Tol Arie
- Phospholipid transfer protein. TI
- SO Current opinion in lipidology, (2002 Apr) 13 (2) 135-9. Ref: 38 Journal code: 9010000. ISSN: 0957-9672.
- ANSWER 19 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. L5
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- ANSWER 21 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. L5

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- AU Gysemans, C. A.; Pavlovic, D.; Bouillon, R.; Eizirik, D. L.; Mathieu, C. [Reprint author]
- TI Dual role of interferon-gamma signalling pathway in sensitivity of pancreatic beta cells to immune destruction.
- SO Diabetologia, (May, 2001) Vol. 44, No. 5, pp. 567-574. print. CODEN: DBTGAJ. ISSN: 0012-186X.
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- SO Nature (London), (13 September, 2001) Vol. 413, No. 6852, pp. 179-183. print.

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- L5 ANSWER 23 OF 50 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Yossuck P; Tadesse Y Y M; Higgins R D (Reprint)
- TI Dexamethasone alters TNF-alpha expression in retinopathy
- MOLECULAR GENETICS AND METABOLISM, (FEB 2001) Vol. 72, No. 2, pp. 164-167. Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.

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- L5 ANSWER 25 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AU Nielsen, Lars Bo. [Reprint author]; Bollano, Entela; Bartels, Emil Daniel
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- AU Livant D L; Brabec R K; Kurachi K; Allen D L; Wu Y; Haaseth R; Andrews P; Ethier S P; Markwart S
- TI The PHSRN sequence induces extracellular matrix invasion and accelerates wound healing in obese diabetic mice.
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- TI Transgenic mice overexpressing insulin-like growth factor-II in beta cells develop type 2 diabetes.
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- TI Long-standing hyperglycemia in C57BL/6J mice does not affect retinal glutathione levels or endothelial/pericyte ratio in retinal capillaries.
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- AU Shankar, K. [Reprint author]; Vaidya, V. S. [Reprint author]; Wang, T. [Reprint author]; Bucci, T. J. [Reprint author]; Mehendale, H. M. [Reprint author]
- TI Diabetic mice are resilient to acetaminophen and thioacetamide hepatotoxicity.
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- TI Expression of Reg and cytokeratin 20 during ductal cell differentiation and proliferation in a mouse model of autoimmune diabetes.
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- AU Molano, R. D. [Reprint author]; Berney, T. [Reprint author]; Ricordi, C. [Reprint author]; Inverardi, L. [Reprint author]
- TI The effects of different enzyme formulations on the outcome of syngeneic transplants of marginal islet mass.
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- L5 ANSWER 36 OF 50 MEDLINE on STN DUPLICATE 16
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- TI Evidence from transgenic mice that interferon-beta may be involved in the onset of diabetes mellitus.
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- AU Anastasi, E. [Reprint author]; Dotta, F.; Tiberti, C.; Ponte, E.; Di Mario, U.
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  CODEN: DBTGAJ. ISSN: 0012-186X.
- L5 ANSWER 41 OF 50 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
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- TI Molecular mapping of the tubby (tub) mutation of mouse chromosome 7.
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- TI Pancreatic expression of antigens for islet cell antibodies in non-obese diabetic mice.
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- TI The Gus-e locus regulates estrogen repression of androgen-induced beta-glucuronidase expression in mouse kidney.
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- L5 ANSWER 48 OF 50 MEDLINE on STN DUPLICATE 24
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- SO Journal of autoimmunity, (1988 Jun) 1 (3) 243-52.

Journal code: 8812164. ISSN: 0896-8411.

(FILE 'HOME' ENTERED AT 16:54:54 ON 23 NOV 2004) FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 16:55:09 ON 23 NOV L12631 S C57BL6 L2774605 S DIABETES OR DIABETIC OR HYPERGLYCEMIA OR HYPOINSULIN? L3110 S L1 AND L2 L42 S REVIEW AND L3 L5 50 DUP REM L3 (60 DUPLICATES REMOVED) L6 2 DUP REM L4 (0 DUPLICATES REMOVED) 71096 S KNOCKOUT(3A) (MOUSE OR MICE) L7 $^{L8}$ 251 S L1 AND L7 L9 8 S L2 AND L8 4 DUP REM L9 (4 DUPLICATES REMOVED)  $L_{10}$ => d bib ab 1-4 l10 L10 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1 AN2004506161 IN-PROCESS DN PubMed ID: 15265871 TТ Activation of the AMP-activated protein kinase by the antidiabetic drug metformin in vivo. Role of mitochondrial reactive nitrogen species. Zou Ming-Hui; Kirkpatrick Stacy S; Davis Bradley J; Nelson John S; Wiles AII Walter G 4th; Schlattner Uwe; Neumann Dietbert; Brownlee Michael; Freeman Michael B; Goldman Mitch H Vascular Research Laboratory, Graduate School of Medicine, University of CS Tennessee, Knoxville 37920, USA.. mzou@mc.utmck.edu Journal of biological chemistry, (2004 Oct 15) 279 (42) 43940-51. SO Journal code: 2985121R. ISSN: 0021-9258. CY United States DTJournal; Article; (JOURNAL ARTICLE) LAEnglish FS IN-PROCESS; NONINDEXED; Priority Journals ED Entered STN: 20041013 Last Updated on STN: 20041027 Metformin, one of the most commonly used drugs for the treatment of type ΔR II diabetes, was recently found to exert its therapeutic effects, at least in part, by activating the AMP-activated protein kinase (AMPK). However, the site of its action, as well as the mechanism to activate AMPK, remains elusive. Here we report how metformin activates AMPK. In cultured bovine aortic endothelial cells, metformin dose-dependently activated AMPK in parallel with increased detection of reactive nitrogen species (RNS). Further, either depletion of mitochondria or adenoviral overexpression of superoxide dismutases, as well as inhibition of nitric-oxide synthase, abolished the metformin-enhanced phosphorylations and activities of AMPK, implicating that activation of AMPK by metformin might be mediated by the mitochondria-derived RNS. Furthermore, administration of metformin, which increased 3-nitrotyrosine staining in hearts of C57BL6, resulted in parallel activation of AMPK in the aorta and hearts of C57BL6 mice but not in those of endothelial nitric-oxide synthase (eNOS) knockout mice in which metformin had no effect on 3-nitrotyrosine staining. Because the eNOS knockout mice expressed normal levels of AMPK-alpha that was activated by 5-aminoimidazole-4-carboxamide riboside, an AMPK agonist, these data indicate that RNS generated by metformin is required for AMPK activation In addition, metformin significantly increased the co-immunoprecipitation of AMPK and its upstream kinase, LKB1, in

C57BL6 mice administered to metformin in vivo. Using

pharmacological and genetic inhibitors, we found that inhibition of either

c-Src or PI3K abolished AMPK that was enhanced by metformin. We conclude that activation of AMPK by metformin might be mediated by mitochondria-derived RNS, and activation of the c-Src/PI3K pathway might generate a metabolite or other molecule inside the cell to promote AMPK activation by the LKB1 complex.

- L10 ANSWER 2 OF 4 MEDLINE on STN
- AN 2004095586 MEDLINE
- DN PubMed ID: 14985314
- TI Effect of PKCbeta on retinal oxygenation response in experimental diabetes.
- AU Luan Hongmei; Leitges Michael; Gupta Rita R; Pacheco Daniel; Seidner Andres; Liggett Jessica; Ito Yasuki; Kowluru Renu; Berkowitz Bruce A
- CS Departments of Anatomy and Cell Biology, Wayne State University, Detroit, Michigan 48201, USA.
- NC R01EY10221 (NEI)
- SO Investigative ophthalmology & visual science, (2004 Mar) 45 (3) 937-42. Journal code: 7703701. ISSN: 0146-0404.
- CY United States
- DT Journal; Article; (JOURNAL ARTICLE)
- LA English
- FS Priority Journals
- EM 200403
- ED Entered STN: 20040302 Last Updated on STN: 20040319
- Entered Medline: 20040318 PURPOSE: To test the hypotheses that, in mice, breathing carbogen (95% AB O(2)-5% CO(2)) oxygenates the retina better than breathing 100% oxygen, the superior hemiretinal oxygenation response to carbogen inhalation is subnormal early in diabetes, and diabetes-induced elevation of retinal protein kinase C (PKC)-beta contributes to this pathophysiology. METHODS: Retinal oxygenation response (DeltaPO(2)) was measured using functional magnetic resonance imaging (MRI) and either carbogen or 100% oxygen inhalation challenge in C57BL/6J control (C) mice. Retinal DeltaPO(2) during carbogen breathing was also measured in PKCbeta knockout (C57BL6-Prkcb1; [KO]), 4 month C57BL/6J diabetic (D), and 4-month diabetic PKCbeta KO (D+KO) Retinal PKCbeta protein expression was assessed by Western analysis. RESULTS: In C mice, retinal DeltaPO(2) during carbogen breathing was significantly greater (P < 0.05) than during oxygen breathing. In D mice, DeltaPO(2) during carbogen breathing was significantly lower than normal in the superior, but not the inferior, hemiretina and was normal (P > 0.0 5) in the KO group. In the D+KO mice DeltaPO(2) was normal (P > 0.05) only at distances less than 1.5 mm from the optic nerve head. PKCbeta expression was elevated in the retina in diabetes (P < 0.05), but was significantly decreased (P < 0.05) in D+KO mice. CONCLUSIONS: The present study confirms that, in the mouse, retinal DeltaPO(2) patterns during different inhalation challenges or in the presence of diabetes are similar to what has been reported in rats. Diabetes-induced elevation of PKC appears to contribute only focally to subnormal retinal DeltaPO(2). This raises the possibility that PKC inhibition therapy may be only regionally effective
- L10 ANSWER 3 OF 4 MEDLINE on STN

DUPLICATE 2

- AN 2002159650 MEDLINE
- DN PubMed ID: 11891415

retinopathy.

- TI Phospholipid transfer protein.
- AU van Tol Arie
- CS Department of Biochemistry, Cardiovascular Research Institute COEUR, Erasmus University Rotterdam, Rotterdam, The Netherlands.. vantol@bcl.fgg.eur.nl

in treating retinal pathophysiology associated with diabetic

SO Current opinion in lipidology, (2002 Apr) 13 (2) 135-9. Ref: 38

Journal code: 9010000. ISSN: 0957-9672.

CY England: United Kingdom

DTJournal; Article; (JOURNAL ARTICLE) General Review; (REVIEW) (REVIEW, TUTORIAL)

English LA

FS Priority Journals

EM200208

EDEntered STN: 20020314 Last Updated on STN: 20020814 Entered Medline: 20020813

- A role for phospholipid transfer protein (PLTP) in HDL remodelling and in AΒ the formation of pre-beta-HDL is now well established, both in vivo and in vitro. Over-expression of human PLTP in C57BL6 mice lowers plasma HDL levels, probably because of increased HDL catabolism. Despite these low HDL levels, plasma from these mice mitigates cholesterol accumulation in macrophages and has increased potential for pre-beta-HDL formation. Plasma HDL concentration is also decreased in PLTP knockout mice. These intriguing observations can be explained by recent studies that indicate that PLTP is not only involved in remodelling of HDL subfractions but also in VLDL turnover. The role of PLTP in atherogenesis and VLDL synthesis was demonstrated in transgenic mouse models with increased susceptibility for the development of atherosclerosis, bred into PLTP knockout mice. data clearly show that PLTP can be proatherogenic. As mentioned above, however, PLTP may have antiatherogenic potential in wild-type C57BL6 mice. Information regarding the role and regulation of PLTP in human (patho)physiology is still relatively sparse but accumulating rapidly. PLTP activity is elevated in diabetes mellitus (both type 1 and type 2), obesity and insulin resistance.
- ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. L10

2001:283432 BIOSIS AN

DN PREV200100283432

- Dual role of interferon-gamma signalling pathway in sensitivity of TIpancreatic beta cells to immune destruction.
- ΑU Gysemans, C. A.; Pavlovic, D.; Bouillon, R.; Eizirik, D. L.; Mathieu, C. [Reprint author]
- LEGENDO, UZ Gasthuisberg O and N, Herestraat 49, B-3000, Leuven, Belgium CS SO

Diabetologia, (May, 2001) Vol. 44, No. 5, pp. 567-574. print. CODEN: DBTGAJ. ISSN: 0012-186X.

DTArticle

LΑ English

Entered STN: 13 Jun 2001 ED Last Updated on STN: 19 Feb 2002

Aims/hypothesis: Disruption of the interferon-gamma (IFN-gamma) signalling AB pathway at the level of interferon regulatory factor-1 (IRF-1) protects islets against cytokine-induced nitric oxide production and cell death in vitro. The aim of this study was to investigate the effects of a global disruption of IFN-gamma signalling, or a selective disruption of IRF-1, on beta-cell sensitivity to in vivo immune destruction. Methods: In a first set of experiments, IFN-gamma receptor knockout mice (IFN-gammaR-/-) and interferon regulatory factor-1 knockout mice (IRF-1-/-) were rendered diabetic by injections of 50 mg streptozotocin i.p. on 5 consecutive days (MLDSTZ). Results: Whereas no difference in sensitivity to MLDSTZ-induced diabetes could be observed between IFN-gammaR-/- mice and their 129/Sv/Ev controls (50% vs 55%, NS), there was an increased incidence of  ${\tt diabetes}$  in IRF-1-/- mice (100% vs 67% in C5781/6 mice, p < 0.05). A similar increased sensitivity to immune destruction of IRF-1-/- islets was observed when these islets were used as allografts. Islet graft survival rate of IFN-gammaR-/- and 129/Sv/Ev islets, when transplanted in alloxandiabetic BALB/c recipients, was comparable (12.0 +- 1.9 days vs 12.9 +- 2.3 days, NS). Allograft rejection, however, of IRF-1-/- islets

by BALB/c recipients occurred more rapidly than following transplantation to their C57Bl/6 controls (9.1 +- 2.0 days vs 13.1 +- 1.5 days, p < 0.003). Conclusions/interpretation: These data indicate that IFN-gamma signal transduction at the beta-cell level is not essential for immune beta-cell destruction in vivo. Moreover, disruption of the IRF-1 gene in pancreatic islets increases susceptibility to beta-cell killing, suggesting that IRF-1 might be necessary for the expression of putative beta-cell "defence and/or repair" genes.

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